Organic LETTERS

Letter

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Direct Synthesis of 2-Aryl-4-quinolones via Transition-Metal-Free Intramolecular Oxidative C(sp^3)−H/C(sp^3)−H Coupling

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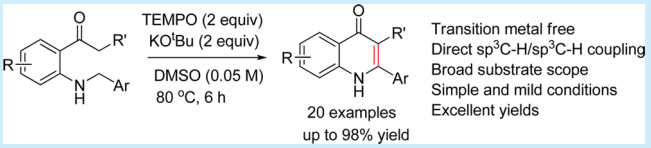
Supporting Information

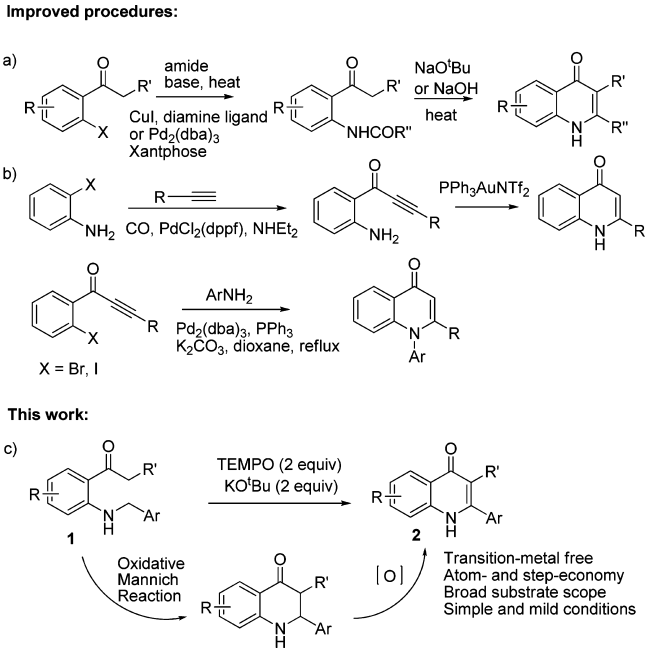
ABSTRACT: A novel, metal-free oxidative intramolecular Mannich reaction was developed between secondary amines and unmodified ketones, affording a simple and direct access to a broad range of 2-arylquinolin-4(1*H*)-ones through C(sp^3)−H activation/C(sp^3)−C(sp^3) bond formation from readily available *N*-arylmethyl-2-aminophenylketones, using TEMPO as the oxidant and KO^{t}Bu as the base.



4-Quinolone has been well recognized as a privileged scaffold prevalent in a vast array of natural products and biologically active compounds,[1] typically constituting an important category of marketed antibacterial agents.[2] More recently, certain 2-substituted-4-quinolones and compounds containing these motifs have been studied as potential treatments for a range of diseases as they exhibit antimitotic,[3] antiviral,[4] antimalarial,[5] xanthine oxidase, and cathepsins inhibitory activities.[6] It is also a versatile synthetic intermediate because the quinolin-4(1*H*)-one contains several reactive centers (positions 1, 3, and 4) for facile derivatization and can also enable different degrees of unsaturation. Therefore, various methods have been developed for the synthesis of this valuable scaffold,[7] and approaches based on cyclocondensation, such as the Niementowski,[8] Conrad−Limpach,[9] and Camps cyclizations,[10] are widely employed. However, most of these methods suffer from harsh reaction conditions (high temperature and/or strong bases or acids) and the limitation of substrate scope. Several improved procedures were reported to make use of transition-metal catalysis[10b,c,11] or tandem reactions from *o*-haloaryl acetylenic ketones/amines or *o*-alkynylbenzamides/aldehydes,[12] providing milder routes toward 2-substituted-4-quinolones (Scheme 1), but still requiring special starting materials, multistep procedures, and long reaction time.

As part of our continuing interest in green chemistry construction of drug-like heterocyclic scaffolds using a cross-dehydrogenative-coupling (CDC) strategy,[13] we recently reported an elegant and robust synthesis for quinazolines and benzimidazoles via metal-free direct oxidative C−H functionalization,[14] featuring straightforwardness, atom-economical nature, and environmental friendliness. As an extension of this approach, herein we report a novel synthesis of diverse 2-aryl-4-quinolone derivatives via a TEMPO-promoted intramolecular oxidative Mannich reaction from simple *N*-arylmethyl-2-aminophenyl ketones (Scheme 1). The oxidative Mannich reaction is an attractive approach to achieve the challenging two C(sp^3)−H bond couplings, with successful examples only on tertiary amines and glycine derivatives as substrates.[13c,d] Almost all tertiary-amine substrates that underwent the CDC reaction efficiently were tetrahydroisoquinoline derivatives. And the glycine derivatives required the assistance of transition-metal catalysts and extra secondary amines. To the best of our knowledge, this is the first report on a transition-metal-free oxidative Mannich reaction between a secondary amine and an unmodified ketone, affording a simple and direct access to a broad range of 2-arylquinolin-4(1*H*)-ones via a tandem oxidative C(sp^3)−H/C(sp^3)−H coupling and aromatization.

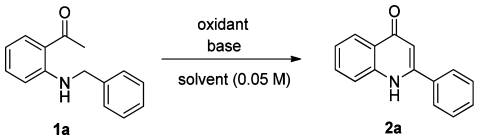
Scheme 1. Synthetic Approaches toward 2-Aryl-4-quinolones



Received: January 26, 2015

DOI: 10.1021/acs.orglett.5b00248
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Condition Screening for the CDC Synthesis of 2-Aryl-quinolones[a,b]



entry	oxidant	base	temp (°C)	solvent	yield[b] % (**2a**)
1	$PhI(OAc)_2$ (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMF	trace
2	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMF	82
3	$Cu(OAc)_2$ (2.0 equiv)	KO^{t}Bu (3 equiv)	120	DMF	3
4	TBHP (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMF	5
5	DDQ (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMF	trace
6	$K_2S_2O_8$ (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMF	44
7	TEMPO (4.0 equiv)	NaOH (4 equiv)	120	DMF	trace
8	TEMPO (4.0 equiv)	K_2CO_3 (3 equiv)	120	DMF	trace
9	TEMPO (4.0 equiv)	Et_3N (4 equiv)	120	DMF	trace
10	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMSO	98
11	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	dioxane	75
12	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	^{t}BuOH	trace
13	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	toluene	47
14	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	DMSO	97
15	TEMPO (4.0 equiv)	KO^{t}Bu (3 equiv)	120	CH_3CN	trace
16	TEMPO (2.0 equiv)	KO^{t}Bu (2 equiv)	80	DMSO	97
17	TEMPO (0 equiv)	KO^{t}Bu (2 equiv)	80	DMSO	68
18	TEMPO (0 equiv)	KO^{t}Bu (2 equiv)	80	DMSO	41[c]
19	TEMPO (2.0 equiv)	KO^{t}Bu (2 equiv)	80	DMSO	93[c,d]

[a]Reaction conditions: **1a** (0.02 mmol, 4 mL solvent), oxidant, and base, 6 h. [b]Yields of isolated products are given. [c]Reaction was performed under an Ar atmosphere. [d]Reaction was completed in 4 h.

Our initial efforts commenced with *N*-benzyl-2-aminoacetophenone **1a** as the model substrate, using $PhI(OAc)_2$ as the oxidant[14a] and KO^{t}Bu as the base (Table 1, entry 1). The starting material was easily synthetic accessible by either reductive amination or nucleophilic substitution of substituted 2-aminoacetophenone, enabling structurally diverse substrate availability. The reaction was performed at 120 °C for 6 h in DMF. Disappointingly, a trace amount of quinolone product was detected, and **1a** was rapidly decomposed to 1-(2-aminophenyl)ethanone. So, the oxidant species was screened first (entries 2−6). Gratifyingly, when TEMPO was used, the desired quinolone product **2a** was obtained in 82% yield (entry 2). Then, careful examination of the solvent and base (entries 2, 7−9, 10−13) revealed that TEMPO in DMSO with KO^{t}Bu served as the best oxidation system, affording **1b** in 98% yield (entry 10). Further survey of the reaction temperature, the equivalents of the oxidant and base, and the reaction time (for the details, please see Supporting Information (SI)) identified entry 16 as an optimized set of conditions, i.e. 2 equiv of TEMPO as the oxidant and 2 equiv of KO^{t}Bu as the base in DMSO at 80 °C for 6 h to deliver the quinolone **2a** in 97% yield. Interestingly, when searching for an optimal equivalence of the TEMPO, the oxidative C(sp^3)−H/C(sp^3)−H coupling reaction still occurred in the absence of the oxidant (entry 17), suggesting the DMSO could serve as an oxidant in this transformation, albeit in a reduced yield. More experiments were performed to explore the role of the oxygen in the two oxidation systems under an Ar atmosphere (entries 18−19). The much lowered yield of the quinolone by the DMSO-only system indicated that the oxygen played an important accelerating role in the transformation while the TEMPO system displayed much higher oxidizing potency.

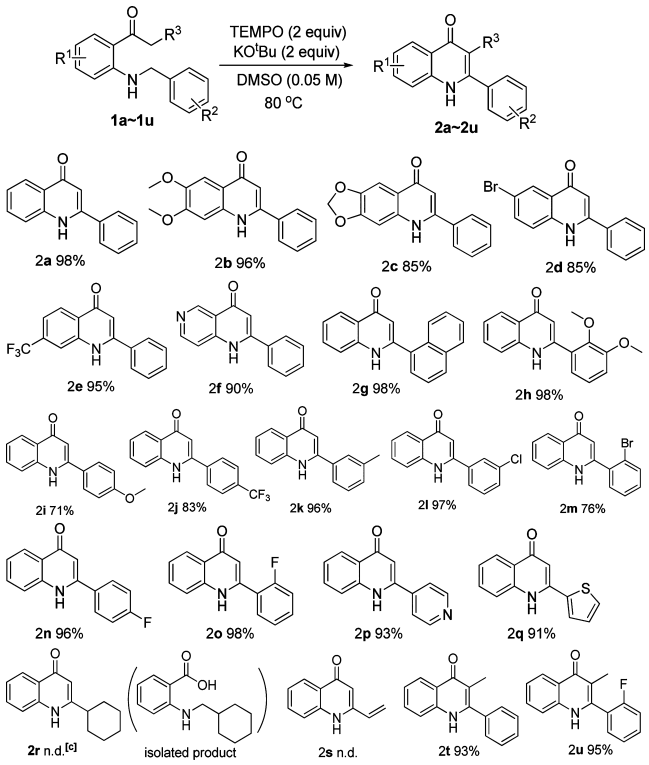
With the optimized conditions in hand, we explored the scope and generality of this oxidative coupling protocol (Scheme 2). We first examined the effect of the R^1 substituent on the acetophenone portion (Scheme 2, products **2a−2f**). In general, both electron-donating and -withdrawing groups on the phenyl ring were well tolerated to give the corresponding quinolones **2a−2e** in good to excellent yields (85%−98%). Even the pyridine analog **1f** was converted to the corresponding 2-phenyl-1,6-naphthyridin-4(1*H*)-one **2f** in 90% yield.

Then, we investigated the R^2 substituent on the benzylamine portion. A diverse array of substrates bearing electron-donating or -withdrawing or sterically hindered group substituted aromatic rings all underwent the oxidative cyclization smoothly and gave the desired 4-quinolone products in excellent yields (Scheme 2, products **2g−2q**), ensuring a broad range of substrate scope. The halogen group had little influence on the reaction (**2l−o**), thus offering the possibility of introducing further substituents by additional coupling reactions. Only the 4-methoxy and 2-bromo group caused a slight decrease in the yield (**2i**, 71%; **2m**, 76%). Heteroaromatic structures were also competent to produce the 2-heterocycle-4-quinolones efficiently (**2p−q**). However, an aliphatic substituent cannot be introduced into the 2-position of 4-quinolone by this protocol (**2r−s**), with the isolation of an oxidized cleavage product, i.e. a benzoic acid derivative instead.

When the 2-aminoacetophenone was extended to 2-aminopropiophenone, i.e. R^3 was the methyl group, the intramolecular oxidative Mannich reaction still proceeded in excellent yields (**2t−u**, 93−95%). It is also worth noting that this protocol was readily scaled up to produce grams of quinolone **2a** without loss of yield, demonstrating the practicability of this procedure (Scheme 3).

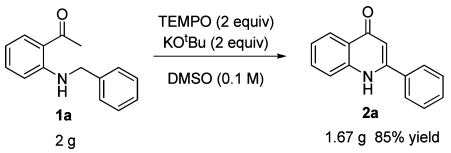
DOI: 10.1021/acs.orglett.5b00248
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope for the Synthesis of Multisubstituted Quinolones via C(sp^3)−H/C(sp^3)−H Oxidative Coupling[a,b]



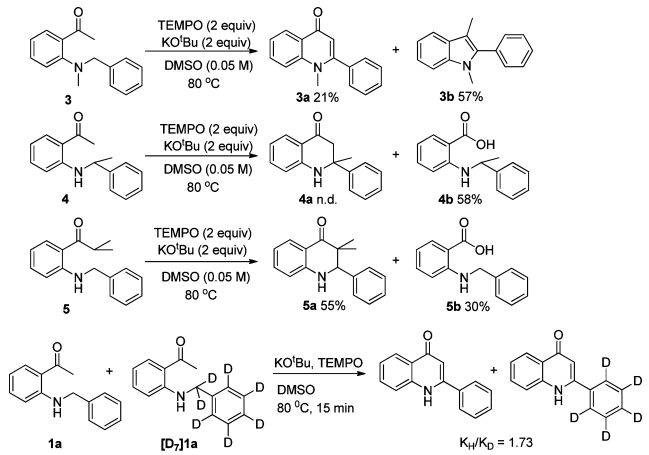
[a]Reaction conditions: **1** (0.5 mmol), KO^{t}Bu (1 mmol), TEMPO (1 mmol), DMSO (10 mL), 80 °C, 6 h. [b]Isolated yields are given. [c]n.d. = not detected.

Scheme 3. Gram-Scale Production of 2-Aryl-4-quinolone



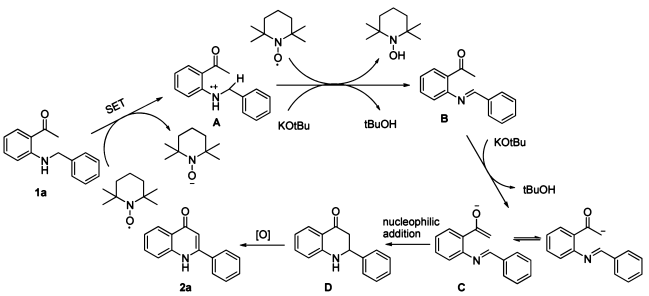
To gain insight into the reaction mechanism, we carried out several control experiments (Scheme 4). First, when *N*-methylated substrate **3** was subjected to the optimized conditions, the quinolone product was obtained in a much lowered yield (**3a**, 21% yield), whereas an indole was harvested as the major product (**3b**, 57%), implying that the N−H is involved in the formation of the quinolone. When a methyl group was appended to the benzylic carbon, the bulky benzylamine **4** failed to generate annulated product **4a**, but gave an overoxidized product benzoic acid **4b** instead, indicating that the steric hindrance on benzylic C−H is critical for the conversion. On the other hand, when the ketone *α*-position was congested by two methyl groups, the resulting isobutyrophenone analog **5** just gave 3,3-dimethyl-2-phenyl-2,3-dihydroquinolin-4(*1H*)-one **5b**, suggesting the quinolone was formed through sequential annulation and aromatization reactions. Notably, the kinetic isotope effect (KIE) (K_H/K_D = 1.73), determined by an intermolecular competition reaction between **1a** and [**D7**]**1a** (see SI for the details), indicated that the cleavage of the benzylic C−H bond was involved in the product-determining step. But the relatively low KIE value suggested a two-step mechanism involving a single electron transfer (SET) from the aniline to TEMPO followed by a hydrogen-transfer step to ultimately form an iminium intermediate.[14b,15]

Scheme 4. Control Experiments



Taken together, a plausible mechanism is proposed in Scheme 5. An anilinium radical cation **A** is generated from an SET process by TEMPO. This radical species facilitates a hydrogen transfer from the adjacent carbon to yield an iminium-type intermediate which is rapidly converted to imine **B** and then to an enolate form **C** under the basic conditions. After a nucleophilic addition to the imine, the annulated product **D** is further oxidized to deliver quinolone product **2a**.

Scheme 5. Proposed Mechanism for the TEMPO-Promoted Oxidative Annulation



In conclusion, we have developed an efficient, mild, and green synthesis of structurally diverse 2-arylquinolin-4(1*H*)-ones through a metal-free oxidative Mannich reaction from readily available *N*-arylmethyl-2-aminophenylketones, using TEMPO as the oxidant and KO^{t}Bu as the base. This is the first construction of a 4-quinolone scaffold via an oxidative direct C(sp^3)−H/C(sp^3)−H coupling under metal-free conditions, featuring atom and step economy, environmental friendliness, and a broad substrate scope.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, reaction conditions screening, compound characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

DOI: 10.1021/acs.orglett.5b00248
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (81325020, 81361120410, 81321092, and 81123004).

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DOI: 10.1021/acs.orglett.5b00248
Org. Lett. XXXX, XXX, XXX−XXX